

## REMARKS

Claims 53-64, 82-97, and 106-108 are pending in the present application. Claims 65-81 and 98-105 stand withdrawn in view of a prior election of species. The claims are presently amended to correct typographical errors, replacing "archael" with "archaeal." These amendments do not narrow the claims or contain new matter.

The Examiner has made a number of objections and rejections which are, for clarity, listed below in the order in which they addressed herein:

- I.** The drawings are objected to because Figures 13-15, 19-21 ,23, 30, 32, 41, 60, 65, 67, 70-A, 71,85,87,89, and 107 respectively contain sequences without SEQ ID NOs;
  - II.** The Sequence Listing is asserted to lack compliance with requirements of the sequence rules (37 CFR 1.821 - 1.825);
  - III.** The specification is objected to with respect to the paragraph reciting prior applications, the descriptiveness of the title; and the alleged use of trademarks;
  - IV.** Claims 53, 56-64, 72-75, 77-95, and 106-108 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No.5,843,669.
  - V.** Claims 53,56-64,82,83,85-95, and 106-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (June 11, 1996), Thompson et al. (1988), and Zhang et al. (1992).
- I.** The drawings are objected to because Figures 13-15, 19-21 ,23, 30, 32, 41, 60, 65, 67, 70-A, 71, 85, 87, 89, and 107 respectively contain sequences without SEQ ID NOs. The descriptions of the drawings are amended herein to include SEQ ID NOs for the sequences appearing in Figures 13-15, 19-21, 30, 32, 41, 60, 65, 67, 70-A, 71, 85, 87, 89, and 107. Figure 23 is amended to include sequence identifiers for the sequences shown. These amendments refer to sequences present in the application at the time of filing and do not contain new matter.
- A complete set of replacement drawings is provided herewith. The replacement drawings have improved clarity and do not contain new matter.

**II.** The Sequence Listing is asserted to lack compliance with requirements of the sequence rules (37 CFR 1.821 - 1.825).

A replacement Sequence Listing is filed herewith as a text file entitled 04447\_ST25.txt. The new sequence listing provides sequences that were present in the application at the time of filing and does not contain new matter.

**III.** The specification is objected to with respect to the paragraph reciting prior applications, the descriptiveness of the title; and the alleged use of trademarks.

- a) The Examiner requests amendment of the first sentence of the specification to reflect that this application is a Divisional of U.S. patent application No. 08/878,653 filed 29 November 1996 issued as U.S. Patent No. 5,843,669 on 01 December 1998 and of U.S. patent Application No. 08/758,314 filed 02 December 1996.

As indicated on the Oath and Declaration copied from the parent case and filed with the instant application on 06/01/2001, the instant application is a Divisional Application of U.S. Appln. Ser. No. 09/308,825, filed Oct. 8, 1999, now U.S. Patent No. 6,562,611, which is a §371 National Entry of PCT US97/21783, filed Nov. 26, 1997, which claims priority to U.S. Patent Appln. No. 08/757,653, filed November 29, 1996, now U.S. Patent No. 5,843,669, and to U.S. Patent Appln. No. 08/758,314, filed December 2, 1996, now U.S. Patent No. 6,090,606.

The Specification is amended herein to recite this cross-reference data in a first paragraph on Page 1.

- b) The Examiner asserts that the title of the invention is not descriptive.

The title of the invention is amended herein to recite "FEN-1 ENDONUCLEASES, MIXTURES AND CLEAVAGE METHODS."

- c) The Examiner notes the use of the trademark TWEEN® in this application, and asserts that it and any other trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

The specification is amended throughout to replace "Tween" and "Nonidet" with "TWEEN" and "NONIDET" and to provide the generic term "detergent" for each mark.

Due to the number of amendments to the Specification, these amendments are made by way of filing a Substitute Specification, provided herewith in marked up and clean form. These amendments do not contain new matter.

**IV.** Claims 53, 56-64, 72-75, 77-95, and 106-108 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No.5,843,669.

As this patent is co-owned with the instant application, Applicants provide herewith a Terminal Disclaimer to obviate this rejection.

The Examiner requests that Applicant identify related copending applications and providing a copy of the current version of claims pending in the those applications that are particularly close to issuance, which raise double patenting issues.

While not acquiescing that U.S. Appln. Ser. No. 11/489,665 raises an issue of double patenting, Applicants nonetheless identify this case and provide the currently pending claims of 11/489,665 as an attachment to this paper. U.S. Appln. Ser. No. 11/489,665 is presently on appeal.

**V.** Claims 53,56-64,82,83,85-95, and 106-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al. (June 11, 1996), Thompson et al. (1988), and Zhang et al. (1992).

It is well-settled law that establishing prima facie obviousness requires *at least* a suggestion of all of the features in a claim. See *In re Wada and Murphy*, citing *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) and *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). See also MPEP §2143. The combination of Wu, Thompson and Zhang fails to teach the features of the instant claims.

Wu et al. teach a FEN-1 endonuclease from human cells. The Examiner admits that Wu et al do not teach the use of an archaeal FEN-1 endonuclease. (Office Action, page 8). The Examiner points to Thompson et al as allegedly teaching an archaeal FEN-1. Thompson

provides no such teaching. Rather, Thompson characterizes a **tRNA Intron Endonuclease** from the *Halobacterium volcanii*. This enzyme is not a FEN-1 flap endonuclease as recited in the instant claims, and Thompson does not teach or suggest anything like a FEN-1 endonuclease from *Halobacterium volcanii* or from any other archaeal organism. The natural substrates for the enzymes taught by Thompson (tRNA precursors) and the natural substrates recognized by flap endonucleases (*e.g.*, displaced flaps in DNA repair) are completely different, and the Examiner has articulated no reasoning as to why one of skill in the art might be prompted to substitute an archaeal tRNA intron endonuclease for a human FEN-1. Even if one did make such a substitution, it does not provide the methods or compositions of the instant claims.

Zhang does not cure this deficiency. Zhang provides nucleic acid structures but does not teach or suggest a purified archaeal FEN-1 endonuclease.

While not acquiescing that the combination of cited art teaches other features of the claims, Applicants submit that the combination of cited art fails to teach or suggest purified archaeal FEN-1 endonucleases, and mixtures and methods of use thereof and therefore fails to render the claims obvious.

Furthermore, a finding of obviousness is appropriate where the cited art provides *all* of the following: a “detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.” (*In re O’Farrell*, 853 F.2d 894, 902 (Fed. Cir. 1988)). While the obviousness calculus is “expansive and flexible” (*KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (U.S. 2007)), the analysis must be founded on a determination that one of skill in the art would have been motivated by a reasonable expectation of success to make the modifications suggested by the examiner (*In re O’Farrell*, 853 F.2d at 904; see *KSR*, 550 U.S. at 421). In evaluating the presence of a reasonable expectation, a result obtained by a “general approach” is not obvious “where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.” (*In re O’Farrell*, 853 F.2d at 903). Consequently, more is required, such as *specific* guidance or a *detailed* description how to achieve the claimed invention. In all cases, the analysis is fact-intensive (see *Graham v. John Deere of Kansas City*, 383 U.S. 1, 17 (U.S. 1966)) and thus requires a “searching” comparison of what is claimed to the cited art (*In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995)).

The cited art would not have provided one of ordinary skill in the art with a reasonable expectation of success in preparing a FEN-1 endonuclease from *H. volcanii*, or in applying it to the methods of Wu. For example, the cited art does not teach or suggest a gene or amino acid sequence for use in isolating or cloning an *H. volcanii* FEN-equivalent protein, nor does the cited art even identify a flap endonuclease *activity* in this organism or characterize conditions under which it might be active or useful. The cited art provides no discussion of what is required, or what should even be considered, to express and/or purify a FEN-1 protein from an archaeal organism, nor of how to use it in a nucleic acid cleavage assay according to the instant claims.

For the reasons recited above, Applicants submit that the cited art fails to establish obviousness of claims 53, 56-64, 82, 83, 85-95, and 106-10, and respectfully request withdrawal of this rejection.

## CONCLUSION

For the reasons set forth above, it is respectfully submitted that all grounds for rejection have been addressed and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 662-1277.

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